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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,885	02/02/2004	Karl Y. Hostetler	UCSD1480-1	1066

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EXAMINER	
MAEWALL, SNIGDHA	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
08/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,885	HOSTETLER ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,14-58,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-12, 14-58 and 62-63.* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicant's Arguments/Remarks and amended claims, filed on 04/23/09 are acknowledged.

Claims 1 and 42 have been amended. Claims 2-4, 13 and 59-61 have been cancelled.

New claims 62-63 have been added.

Accordingly, claims pending in this application are **1, 5-12, 14-58 and 62-63.**

Claim Rejections - 35 USC § 112

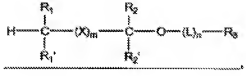
2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

3. Claims 1, 5-12, 14-58 and 62-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

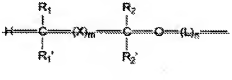
1. (Currently amended) A method for treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex with ocular tissue, wherein the complex has the structure I:



I

~~is formed by covalently attaching a moiety to a therapeutically active agent~~

wherein the pathological condition is selected from a the group consisting of macular degeneration, eye trauma, a pre-existing retinal detachment, ocular proliferative or vascular diseases, or diseases of elevated intraocular pressure or inflammation, ~~with the further proviso that the moiety is selected from a group consisting of sulfates, sulfonates, phosphates, lipids, phospholipids, carboxylates, sulfosuccinates, arginine esters, cholesterol esters, carbamates, carbonates, ketals, and the moiety having structure (I):~~



(I)

wherein in structure I:

each of R_1 and R_1' is independently selected from a the group consisting of –H, an optionally substituted –O(C_1-C_{24})alkyl, –O(C_1-C_{24})alkenyl, –O(C_1-C_{24})acyl, –S(C_1-C_{24})alkyl, –S(C_1-C_{24})alkenyl, and –S(C_1-C_{24})acyl, wherein at least one of R_1 and R_1' is not –H, and wherein the alkenyl or acyl optionally has between 1 and 6 double bonds,

each of R_2 and R_2' is independently selected from a the group consisting of –H, an optionally substituted –O(C_1-C_7)alkyl, –O(C_1-C_7)alkenyl, –S(C_1-C_7)alkyl, –S(C_1-C_7)alkenyl, –O(C_1-C_7)acyl, –S(C_1-C_7)acyl, –N(C_1-C_7)acyl, –NH(C_1-C_7)alkyl, –N((C_1-C_7)alkyl)$_2$, oxo, halogen, –NH_2, –OH, and –SH;

X is

L is selected from a the group consisting of a valence bond and a bifunctional linking group of the formula –J–(CR_2)$_t$–G–, wherein t is an integer having the value between 1 and 24, each of J and G is independently selected from a the group consisting of –O–, –S–, –C(O)O–,and –NH–, and R is selected from a the group consisting of –H, substituted or unsubstituted alkyl, and alkenyl;

R_3 is a phosphate or phosphonate derivative of a therapeutically active agent;

m is an integer having the value between 0 and 6; and

n is 0 or 1,

thereby treating the pathological condition.

Wherein R3 is a phosphate or phosphonate derivative of a therapeutically active agent is not seen to be disclosed in specification. Accordingly it is a new matter. Additionally no such structure of complex is also shown to be disclosed in the disclosure.

Response to Arguments

4. Applicant's arguments filed 04/23/09 have been fully considered but they are not persuasive.

Applicant directs to paragraph 0037 and argues that there is support for R3 limitation. Applicant's arguments are not persuasive because the specification discloses R3 as therapeutic agent rather than a phosphate or phosphonate derivative of therapeutic agent. It is to be noted that claim 1 recites "R" which has no support in specification, Examiner suggests replacing "R" with 'R2".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 5-12, 14-15 and 22-52 and 62-63 are rejected under 35 U.S.C. 103(a)

as being unpatentable over Cheng et al. (Feb. 2002) (herein onwards Cheng et al. I). (Investigative Ophthalmology & Visual Science, Feb. 2002, Vol. 43).

Cheng et al. disclose the intraocular drug delivery system using the free crystalline lipid prodrug of ganciclovir, HDP-P-GCV, as a prototype. Cheng et al. discloses a local intravitreal drug administration for vitreoretinal diseases, which bypasses the blood-ocular barriers and allows higher intraocular drug levels and avoids many side effects associated with systemic therapy. The intraocular drug delivery may also provide constant and slow release drug. Cheng et al. further disclose that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, **retinal detachment**, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles may have utility in treating or preventing HSV retinitis when injected intravitreally as Infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). The local retinal or lens toxicity observed with high doses may be eliminated, and antiviral duration could even be prolonged by using smaller drug particles, which may provide a better release rate and require less drug to maintain a therapeutic vitreous level with the advantage of a smaller drug depot (see page 521, 4th paragraph and column 2, first paragraph).

Cheng's references teach that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, retinal

detachment, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles have utility in treating or preventing HSV retinitis when injected intravitreally as infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). Retinitis can be characterized as one of the conditions of eye trauma, therefore Cheng's references renders the claimed limitations obvious.

Furthermore, under treatment study, the reference discloses animal study of rabbits with severe conditions of retinitis which shows whole retina involvement with retinal detachment and severe vitreous clouding, see page 516, column 2 second paragraph and treatment studies show retinitis was delayed and was significantly severe in the drug treated eyes than in control eyes, see page 517, prophylaxis results. The reference thus renders the claimed invention obvious.

7. Claims 1, 5-12, 14-15, 22-52 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (May 2000). (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6).

Cheng et al. disclose that Cytomegalovirus (CMV) infection of the retina is the most common infection in acquired immune deficiency syndrome (AIDS) patients. (See page 1523, first paragraph).
Ganciclovir (GCV) was the first drug to be approved for CMV infection in AIDS

patients. Ganciclovir is effective in treating CMV retinitis by intravenous administration, but the drug does not eliminate the virus from the retina, requiring long-term suppressive maintenance therapy. Systemic toxicity such as bone marrow suppression was also a problem. The sustained-release GCV implant is effective treatment for CMV retinitis and recurrent CMV retinitis, but complications from surgery such as endophthalmitis and retina detachment are sight threatening. Therefore, in an effort to overcome the disclosed threat, Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and long-lasting for treatment of CMV retinitis (page 1523, column 2, paragraph 2 and 3).

Cheng et al. further disclose the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinisis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. This type of self-assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases (page, 1531, last paragraph).

Because Cheng's references discloses the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinitis, page 1524) and disclose that the antiviral

agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. Retinitis can be characterized as one of the conditions of eye trauma, therefore, Chengs references renders the claimed limitations obvious.

Furthermore, the reference teaches that pathologic evaluation of eyes with retinitis showed retinal detachment, destruction of whole layers of retina with retinal cell necrosis accompanied by severe choroiditis and optic nerve inflammation, see page 1528 first paragraph and figure 6. Since the reference teaches treatment of retinitis with the claimed compound, one of ordinary in the art would have envisaged treating other pathological diseases and conditions such as retinal detachment, vitritis or choroiditis with the claimed compound.

8. Claims 16-21 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cheng et al.) or (Cheng et al. I); (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6 and Feb. 2002, Vol. 43) as cited above in view of Unger (US Patent No. 6,120,751).

The teachings of Cheng et al. have been discussed above. Cheng et al. do not exclusively teach various nucleosides, antibody or AZT.
Unger discloses compositions comprising charged lipids, targeting ligands and the use of such compositions in drug delivery, targeted drug delivery, therapeutic imaging and diagnostic imaging as well as their use as contrast agents (abstract). The composition comprises various nucleosides, antibody, polyclonal antibody, fab fragments and AZT

(column 45 and 46, lines 67 and 1 and column 48, lines 18-25).

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to incorporate various therapeutic agents such as various nucleosides as cited above in the formulation of Cheng et al. since Cheng et al. suggest that assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases and Unger teaches that such a composition comprising nucleosides help in targeted delivery. A skilled artisan would have had a reasonable expectation of success in treating pathological condition of ocular tissue with a composition comprising therapeutic agents such as nucleosides.

Response to Arguments and Declaration

9. Applicant's arguments filed 04/23/09 have been fully considered but they are not persuasive.

Applicants argue that Applicants have provided a Declaration under Rule 132 from Dr. William R. Freeman. As stated in the Declaration, retinitis is a disease characterized by the inflammation of the retina, e.g., caused by cytomegalovirus infection or by other infection. The term "retinitis" does not include "trauma," that is how those skilled in the art refer to a mechanical injury to an eye cause by some kind of blow or impact. The Declaration, therefore, clearly establishes that it would not be proper to extend the treatments used for retinitis to be used to treat traumas. Also, please note that the claims have been amended and inflammation is no longer recited, thus even

more clearly distinguishing the present claims from the cited references (the Examiner stated that inflammation is related to retinitis).

Applicant's arguments are not persuasive because claims have been given broadest reasonable interpretation. The dictionary definition of "trauma by Merriam Webster dictionary (http://www.merriam-webster.com/dictionary/trauma) is "an injury to tissue caused by extrinsic agent". Applicants themselves state that "in medical usage, retinitis is a disease characterized by the inflammation of the retina, e.g., caused by cytomegalovirus infection or by other infection.

Thus retinitis does read on "eye trauma" because it is caused by extrinsic agent such as cytomegalovirus. As such the declaration filed on 04/23/09 is insufficient to overcome the rejection of record.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612